REMARKS/ARGUMENTS

Claims 1-7 are pending in this application. Claims 1-7 are rejected in the Office action of June 1, 2006. Claim 1 is hereby amended for clarification, no new matter is added by this amendment. In view of the remarks made herein, Applicants respectfully request reconsideration of claims 1-7.

Rejections under 35 U.S.C. § 103(a)

Claims 1-7 are rejected under 35 U.S.C. § 103(a) over Cleland *et al.* (US Pat. No. 5,643,605, hereinafter referred to as "Cleland.") Applicants respectfully disagree. While Cleland does disclose compositions and methods for encapsulating adjuvants or biologically active agents in microsphere compositions, the methods disclosed in Cleland are not the same as recited in claim 1. Specifically, Cleland does not teach or suggest blending a pore forming agent selected from the group consisting of PEG, poloxamer, and combinations thereof, with the PLGA polymer solution at a level from 10% to 30% (w/w, pore forming agent/polymer) to provide a resulting solution comprising the polymer and pore forming agent as recited in claim 1. Applicants' claims call for first, forming the polymer solution, then adding the pore forming agent, then dispersing the biologically active agent in that solution, then solidifying to form the microspheres. The effect of this process is that the PEG and/or poloxamer act as a pore forming agent as the microspheres biodegrade.

Cleland's method, on the other hand, involves first, dissolving PLGA in an organic solvent to produce a solution, adding an aqueous adjuvant solution to that organic solution, and then adding the solution to an emusification bath to produce microspheres. Any PEG or poloxamer in Cleland, if used at all, is added to the aqueous adjuvant solution, for the purpose of protecting the adjuvant from the organic solvent. (Cleland, column 8, lines 63-66). The only time Cleland suggests the use of PEG and/or poloxamer is as *excipients* to stabilize the adjuvant during encapsulation, in amounts suitable for that purpose. Cleland does not teach or suggest adding PEG and/or poloxamer directly to the polymer in an amount necessary to act as a pore-forming agent.

Moreover, the amounts of PEG and/or poloxamer taught by Cleland is different from that claimed by Applicants. Comparing the 0.1% to 30% (w/v) based on antigen solution of Cleland to the 10% to 30% (w/w) based on polymer of Applicants is like comparing apples to oranges. These amounts are based on completely different values and cannot be compared directly.

Cleland is adding excipient based on antigen solution, Applicants are adding pore forming agents based on the amount of the polymer. Because Cleland is using the excipient to stabilize the antigen prior to encapsulation, rather than adding the excipient to the polymer itself, these percentages cannot be compared directly. While the examples of Cleland do not use PEG and/or poloxamer as excipients, the highest amount of excipient disclosed in Cleland is 30% (w/v), or 0.3g excipient/mL adjuvant solution. (Cleland, column 9, lines 33-34). In other words, Cleland suggests that 0.001-0.3 g of excipient may be added per mL of adjuvant solution, without showing the addition of any PEG or poloxamer in any amount in the examples and with no teaching or suggestion of how much of that excipient may be encapsulated.

The Examiner asserts in the Office Action of June 1, 2006 that the 0.1-30% of the prior art overlaps the 10-30% claimed by Applicants. (Office Action of June 1, 2006, page 4, last paragraph.) As shown above, Cleland's 0.1-30% (w/v) based on antigen solution is not the same as Applicants' claimed range of 10-30% (w/w) based on weight of polymer. Furthermore, Applicants have shown that the specific claimed range produces unusual/unexpected results. As shown in Applicants' specification, when less that 10% (w/w) PEG, based on the weight of PLGA, was used in the polymer microspheres, a significant amount of the encapsulated BSA was not released, due to aggregation of the BSA from low microclimate pH. (See, Applicants' specification, paragraphs 145 and 154). At levels less than 10% (w/w), there was not enough PEG to maintain the microclimate pH. (See, Applicants' specification, paragraphs 145 and 154). At 20% (w/w) PEG, the protein release was significantly greater, and pH was maintained such that no protein aggregation or peptide-hydrolysis was observed. (See, Applicants' specification, paragraphs 145 and 154). Finally, at 30% (w/w) PEG, a higher burst release was observed, effectively setting the upper limit because once the burst release is too great, the microspheres will not last for 4 weeks. (Applicants' specification, paragraph 145). In other words, Applicants have shown that using PEG in amounts outside of the claimed 10% to 30% (w/w) range recited in claim 1 will not produce the desired pore forming effect. Applicants have shown that using amounts outside of that range will not effectively maintain the microclimate pH at greater than 3 for at least 4 weeks.

Next, the Examiner notes in the Office Action of June 1, 2006, that pH of Cleland's formulation ranges from about 5-8. (Office Action of June 1, 2006, page 3, carryover paragraph). As noted by the Examiner, this is the **pH of the formulation**. This is the pH as the

microspheres are formed, not the pH as the microspheres biodegrade, as recited in Applicants' claim 1. Because Applicants' rely on the PEG or poloxamer, in an amount of 10-30% (w/w) based on the weight of the polymer to maintain the pH during biodegradation, and Cleland does not teach the use of PEG or poloxamer in that range, one cannot assume that the microspheres of Cleland maintain the same pH during degradation as they do during formation. As shown by Applicants in their specification, when less that 10% (w/w) PEG, based on the weight of PLGA, was used, a significant amount of the encapsulated BSA was not released, due to aggregation of the BSA from low microclimate pH. At levels less than 10% (w/w), there was not enough PEG to maintain the microclimate pH. (See, Applicants' specification, paragraphs 145 and 154). At 20% (w/w) PEG, the protein release was significantly greater, and pH was maintained such that no protein aggregation or peptide-hydrolysis was observed. (See, Applicants' specification, paragraphs 145 and 154). Cleland's 0.1% to 30% (w/v) excipient simply does not provide enough PEG and/or poloxamer to maintain the microclimate pH.

Finally, the Examiner looks to the molecular weights of the PEGs and poloxamers. However, as explained above, the difference between Cleland and the Applicants' claimed invention is the actual amount of PEG and/or poloxamer used. Because Cleland does not teach or suggest using PEG and/or poloxamer in the range from 10% to 30% (w/w), Applicants respectfully submit that claim 1, and claims 2-7 dependent thereon are patentable over Cleland.

In conclusion, in light of the amendments and the remarks made herein, Applicants submit that claims 1-7 are now in condition for allowance. Prompt notice of such allowance is respectfully requested.

Respectfully submitted,

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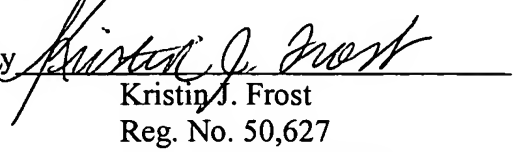
By 

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